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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,275	08/01/2005	Wei-Ping Min	4767-217 LAB	9949

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
10/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,275	MIN ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *1-21,23,25,26,32-46 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,24,27,47-49, 51-53 and 55-61* is/are rejected.

7)☐ Claim(s) *28-31 and 54* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 07/25/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 02/27/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 02/27/2008, claims 1-61 are pending in the application. Applicant has pointed out to Examiner that claims 58-60 recite antigen presenting cell types and are directed to the elected invention and should be examined. Claims 58-60 are directed to the elected invention and were inadvertently withdrawn as being drawn to an elected invention and therefore will be examined in the office action along with the elected invention. Additionally, after further consideration, claims 28-31, 49, 51, 52 and 54 were inadvertently withdrawn as being drawn to an elected invention and are directed to the instant invention and will be examined in the office action along with the elected invention. Claims 1-21, 23, 25, 32-46 and 50 are withdrawn as being drawn to a non-elected invention.

New Claim Objections and Rejections

Claim Objections

Claims 28-31 and 54 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and/or cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 28-31 have not been further treated on the merits. Applicant should note that if claims 28-31 were amended to the proper form, the claims would be rejected under 35 U.S.C. 101 and 112 because of the claimed recitation of a use, which without setting forth any steps involved in the process, results in an improper definition of a process.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47, 51, 55 and 57-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 47, 51, 55 and 57-60 are drawn to method for decreasing immunogenicity and rejection potential of an organ for transplantation, said method comprising perfusing into said organ at least one construct that suppresses T-cell activity and inhibits the

expression of an endogenous target gene encoding a cytokine, wherein the construct is an siRNA.

The specification as filed discloses siRNA molecules targeted to IL-12 and IFN-gamma (Example 2). The specification discloses prophetic methods of inhibiting cytokines to treat a variety of immune disorders (see pages 23-25). The specification does not provide adequate written description of a construct that targets any cytokine wherein this construct suppresses T cell function and further provide a treatment of transplant rejection of any organ in a mammalian subject. The specification does not provide adequate written description of any siRNA molecule that targets any cytokine such that T cell suppression occurs and further provides treatment of transplantation rejection of any organ in any mammalian subject. Because the instant invention is drawn to a method of treatment of an immune disorder and transplantation rejection by inhibiting the expression of a cytokine, it follows logically that a method of using any composition comprising a construct cannot be adequately described without describing the construct.

The specification fails to provide any structure or sequence that would impart the recited activity of inhibition of any cytokine expression such that T cell suppression and treatment of transplant rejection of any organ occurs. Further, the specification does not provide any specific examples or an adequate number of species to represent the claimed genus of constructs capable of inhibition of any cytokine.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, “An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that “[w]ithout such disclosure, the claimed methods cannot be said to have been described.”)

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention because the specification, while providing information on several siRNA molecules targeted to IL2 and IFN gamma, does not provide any other information or guidance as

to what construct or what siRNA construct targeted to any cytokine sequence would inhibit cytokine expression and further suppress T cell activity such that treatment of transplantation rejection occurs.

Response to Applicant's arguments will be addressed as they pertain to the new claim rejection above. Applicant argues that it is clear that the claimed invention is directed to the targeting a cytokine and the targeted molecules are clearly specified to be those produced within an antigen presenting cell and the skilled artisan is readily able to prepare nucleic acid constructs or more specifically siRNA constructs which can target cytokines. The Applicant further argues the claimed invention is distinguished from the cited case law of *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) because at least two specific compounds have been exemplified.

Applicant's arguments are not convincing. While the skilled artisan may be readily able to prepare nucleic acid constructs and more specifically siRNA constructs which can target cytokines, the claims are broadly drawn to any construct that targets any cytokine, known or yet to be discovered, produced by an antigen presenting cell. The claimed composition embraces any construct that encodes for any molecule that is capable of inhibiting expression of any cytokine produced in any antigen presenting cell. The exemplification of a siRNA targeted to IL-12 and IFN-gamma are not an adequate umber of species within the genus of constructs to constitute a description of the entire genus claimed. Thus, the instantly claimed invention cannot be said to have been

adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 55 and 57-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Kato et al. (PNAS 1996, Vol. 93, pages 9085-9089).

The instant claim is drawn to a method for treatment of a immune disorder characterized by inappropriate T cell activity in a mammalian subject comprising

administering a composition that comprises at least one construct that possess specific homology to part of a gene encoding a cytokine produced within an antigen presenting cell, wherein the immune disorder is multiple sclerosis or transplant rejection for example (see claim 57) and wherein the antigen presenting cell is a dendritic cell.

Kato et al. teach the IL-12p40 subunit has immunosuppressive effects and making a construct comprising the IL-12p40 gene (see page 9085, second column). Kato et al. teach increased survival of myoblast transplantation after administration of the IL-12p40 construct in myoblast cells transplanted into murine subjects and concludes that locally produced IL-12 is effective at preventing graft rejection (see page 9086). Kato et al. demonstrate a decrease in Th1 and CTL cells in mice given the construct comprising an IL-12p40 subunit (see page 9087).

Thus, Kato et al. anticipates claims 55 and 57-60 of the instant invention.

Claims 47, 48, 49, 51-53 and 55-61 are rejected under 35 U.S.C. 102(e) as being anticipated by Qian et al. (US 2004/0043483) as evidenced by Li et al. (Journal of Immunology 2001, Vol. 166: pages 5619-5628).

The instant claims are drawn to a method for treatment of a immune disorder characterized by inappropriate T cell activity in a mammalian subject comprising administering a composition that comprises at least one construct that possess specific homology to part of a gene encoding a cytokine produced within an antigen presenting cell or a siRNA targeted to a cytokine gene, wherein the immune disorder is transplant rejection and wherein the antigen presenting cell is a dendritic cell.

For purposes of applying art, the limitation in the method reciting 'administering a composition comprising a construct' would encompass administering cells comprising said construct as discussed below. Additionally, the instant specification does not define "perfusing said organ" and therefore for purposes of prior art 'perfusing' is interpreted to mean the composition is administered through or over the organ such as by any route.

Qian et al. teach a method of preventing or minimizing transplant rejections or autoimmune diseases comprising genetically engineering dendritic cells with constructs comprising antisense compounds, ribozymes or gene silencing methods (which would encompass siRNA) encoding endogenous genes such as IL-12, wherein the constructs may be introduced into the cells by vectors (see page 6, particularly paragraphs 0091-0094). Qian et al. teach compositions of said cells along with a pharmaceutically acceptable carrier for administration to a subject that can be administered by conventional routes such as intramuscular, intra-atrial, intraperitoneal or intravenous (see paragraphs 0096-0102). As evidenced by Li et al., decreasing the activity of IL-12 produced from dendritic cells promotes T cell apoptosis, which would be considered suppressing T cell activity, which is responsible for rejection of organs and tissue (see page 5626).

Thus Qian et al. anticipates claims 47, 48, 49, 51-53 and 55-61 the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 22, 24, 27, 47-49, 51-53 and 55-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robbins et al. (US Patent No. 6,936,468), Li et al. (Journal of Immunology 2001, Vol. 166: pages 5619-5628), Hammond et al. (Nature Reviews Genetics February, 2001 cited on PTO 892 mailed 05/21/2007) and Tuschl et al. (WO 02/44321 cited on PTO 892 mailed 05/21/2007).

The instant claims are drawn to a method for treatment of an immune disorder and rejection potential of an organ for transplantation, said method comprising perfusing into said organ or administering to a mammal at least one construct that suppresses T cell activity, wherein said construct inhibits the expression of an endogenous target gene encoding a cytokine produced in an antigen presenting cell, wherein the construct is a siRNA and wherein the antigen presenting cells are dendritic cells.

For purposes of applying art, the method of administering a composition comprising a construct would encompass administering cells comprising said construct as discussed below. Additionally, t he instant specification does not define “perfusing said organ” and therefore for purposes of prior art ‘perfusing’ is interpreted to mean the composition is administered through or over the organ such as by any route.

Robbins et al. teach a method of regulating the immune response in a mammalian host comprising introducing tolerogenic dendritic cells into said host. Robbins et al. teach administration of tolerogenic dendritic cells are useful for prolonging graft survival and useful for inhibiting the inflammatory responses that lead to disease (see column 1). Robbins et al. teach inhibiting the expression or activity of the transcription factor, NF-kB, using an oligonucleotide targeted to a gene encoding NF-kB (see column 1 and Examples 6 and 7). Robbins et al. teach the cells can be produced to comprise an construct expressing an oligonucleotide that is targeted to a NF-kB gene and further teach compositions of said cells along with a pharmaceutically acceptable carrier for administration to a subject that can be administered by conventional routes such as intramuscular, intra-atrial, intraperitoneal or intravenous (see column 10). Robbins et al. do not teach a construct that inhibits expression of a cytokine produced from an antigen presenting cell such that suppression of T cell activity occurs and do not teach the construct is siRNA.

Li et al. teach the cytokine IL-12, which is produced from antigen presenting cells such as dendritic cells, plays a key role in the regulation of alloimmune responses. Li et al. teach neutralization of IL-12 activity effectively reversed acute liver graft rejection (see page 5625 and Figure 2). Li et al. teach decreasing the activity of IL-12 produced from dendritic cells promotes T cell apoptosis, which would be considered suppressing T cell activity that is responsible for rejection of organs and tissue (see page 5626).

Hammond et al. teach two methods for silencing specific genes: antisense and RNA interference. Hammond et al. teach that although antisense methods are

straightforward techniques for probing gene function, the methods have suffered from "…questionable specificity and incomplete efficacy." (see page 110, column 1). Hammond et al. further teach " "…dsRNAs have been shown to inhibit gene expression in a sequence-specific manner" and further "RNAi is a potent method, requiring only a few molecules of dsRNA per cell to silence expression."

Tuschl et al. teach siRNA molecules and teach compositions comprising siRNA and an acceptable carrier that are capable of silencing gene expression (see page 9, lines 17-25). Tuschl et al. teach siRNA molecules can be designed to target any gene and can be made in expression constructs and vectors that are capable of being delivered to any cell (see page 7). Tuschl et al. teach that siRNAs represent a new alternative to previous therapeutics using inhibitory molecules.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to introduce a construct targeted to IL-12 in the method taught by Robbins et al. and further obvious to use siRNA as the construct.

One of ordinary skill in the art would have wanted to target IL-12 in methods of treatment that prevent transplant rejection and inhibit the inflammatory responses of IL-12 in autoimmune diseases. Because it is well known to the skilled artisan that host T-cell activity is detrimental to the survival of transplanted organs and tissues and given that Li et al. teach IL-12 plays key role in the regulation of alloimmune responses and inhibiting the activity of IL-12 promotes T cell apoptosis, one would have wanted to use dendritic cells that have oligonucleotides that inhibit the expression and activity of IL-12 in a treatment to promote the survival of transplanted organs and tissues.

In choosing an inhibitory oligonucleotide, one would have wanted to make and use a siRNA targeted to an IL-2 cytokine gene because it was well known at the time the invention was made that siRNA molecules are efficient molecules to target and decrease expression of a target gene and because Hammond et al. teach using siRNA to inhibit gene expression is effectively more sequence specific than using other inhibitory compounds such as antisense molecules and RNAi using dsRNA is a more potent method requiring only a few molecules of dsRNA per cell. One of ordinary skill in the art would have wanted to make the siRNA to possess specific homology to the entire exon region of a gene encoding IL-12 and it would have been a matter of routine experimentation to design such a molecule in order to efficiently target the expression of IL-12. One would have been motivated to create such compounds with increased functionality, and since siRNAs are taught by Tuschl et al. as being useful in silencing gene expression, one would have looked to Tuschl et al. as a guide to design a siRNA targeted to IL-12.

One would have a reasonable expectation of success given that Tuschl et al. teach how to make and use virtually any siRNA to any gene provided the target sequence is known and teach that methods of RNA synthesis are known in the art, as evidenced by the examples provided therein and one would have expected to be able use a dendritic cell comprising an siRNA in the methods of treatment of an immune disorder as shown by Robbins et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 101 and 35 USC § 112

The rejection of claims 22, 24 and 27 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in response to the claim amendments filed 07/25/2008.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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